leukemia and myelodysplastic syndromes (Chapter 13), which can have identical clinical manifestations. In aplastic anemia, the marrow is hypocellular (and usually markedly so), whereas myeloid neoplasms are associated with hypercellular marrows filled with neoplastic progenitors.

The prognosis is variable. Bone marrow transplantation is the treatment of choice in those with a suitable donor and provides a 5-year survival of more than 75%. Older patients or those without suitable donors often respond well to immunosuppressive therapy.

Pure Red Cell Aplasia

Pure red cell aplasia is a primary marrow disorder in which only erythroid progenitors are suppressed. In severe cases, red cell progenitors are completely absent from the marrow. It may occur in association with neoplasms, particularly thymoma and large granular lymphocytic leukemia (Chapter 13), drug exposures, autoimmune disorders, and parvovirus infection (see later). With the exception of those with parvovirus infection, it is likely that most cases have an autoimmune basis. When a thymoma is present, resection leads to hematologic improvement in about half of the patients. In patients without thymoma, immunosuppressive therapy is often beneficial. Plasmapheresis may also be helpful in unusual patients with pathogenic autoantibodies, such as neutralizing antibodies to erythropoietin that appear de novo or following the administration of recombinant erythropoietin.

A special form of red cell aplasia occurs in individuals infected with parvovirus B19, which preferentially infects and destroys red cell progenitors. Normal individuals clear parvovirus infections within 1 to 2 weeks; as a result, the aplasia is transient and clinically unimportant. However, in persons with moderate to severe hemolytic anemias, even a brief cessation of erythropoiesis results in rapid worsening of the anemia, producing an aplastic crisis. In those who are severely immunosuppressed (e.g., persons with advanced HIV infection), an ineffective immune response sometimes permits the infection to persist, leading to chronic red cell aplasia and a moderate to severe anemia.

Other Forms of Marrow Failure

Myelophthisic anemia **describes a form of marrow failure in which space-occupying lesions replace normal marrow elements.** The commonest cause is metastatic cancer, most often carcinomas arising in the breast, lung, and prostate. However, any infiltrative process (e.g., granulomatous disease) involving the marrow can produce identical findings. Myelophthisic anemia is also a feature of the spent phase of myeloproliferative disorders (Chapter 13). All of the responsible diseases cause marrow distortion and fibrosis, which act to displace normal marrow elements and disturb mechanisms that regulate the egress of red cells and granulocytes from the marrow. The latter effect causes the abnormal release of nucleated erythroid precursors and immature granulocytic forms *(leukoerythroblastosis)* into peripheral smears, and the appearance of *teardrop-shaped red cells*, which are believed to be deformed during their tortuous escape from the fibrotic marrow.

Chronic renal failure**, whatever its cause, is almost invariably associated with an anemia that tends to be roughly proportional to the severity of the uremia.** The basis of anemia in renal failure is multifactorial, but the dominant cause is the diminished synthesis of erythropoietin by the damaged kidneys, which leads to inadequate red cell production. Other contributors are an extracorpuscular defect that reduces red cell life span, and iron deficiency due to platelet dysfunction and increased bleeding, which is often encountered in uremia. Administration of recombinant erythropoietin results in a significant improvement of the anemia, although an optimal response may require concomitant iron replacement therapy.

Hepatocellular liver disease, whether toxic, infectious, or cirrhotic, is associated with anemia attributed to decreased marrow function. Folate and iron deficiencies caused by poor nutrition and excessive bleeding often exacerbate anemia in this setting. Erythroid progenitors are preferentially affected; depression of the white cell count and platelets is less common but also occurs. The anemia is often slightly macrocytic due to lipid abnormalities associated with liver failure, which cause red cell membranes to acquire phospholipid and cholesterol as they circulate in the peripheral blood.

Endocrine disorders, particularly hypothyroidism, may also be associated with a mild normochromic, normocytic anemia.

KEY CONCEPTS

Megaloblastic Anemia

- Caused by deficiencies of folate or vitamin B_{12} that lead to inadequate synthesis of thymidine and defective DNA replication
- Results in enlarged abnormal hematopoietic precursors (megaloblasts), ineffective hematopoiesis, macrocytic anemia, and (in most cases) pancytopenia
- B_{12} deficiency also associated with neurologic damage, particularly in the posterior and lateral tracts of the spinal cord

Iron Deficiency Anemia

- Caused by chronic bleeding or inadequate iron intake; results in insufficient hemoglobin synthesis and hypochromic, microcytic red cells

Anemia of Chronic Disease

- Caused by inflammatory cytokines, which increase hepcidin levels and thereby sequester iron in macrophages, and also suppress erythropoietin production

Aplastic Anemia

- Caused by bone marrow failure (hypocellularity) due to diverse causes, including exposures to toxins and radiation, idiosyncratic reactions to drugs and viruses, and inherited defects in telomerase and DNA repair

Pure Red Cell Aplasia

- Acute: Parvovirus B19 infection (may persist in immunosuppressed patients)
- Chronic: Associated with thymoma, large granular lymphocytic leukemia, presence of neutralizing antibodies against erythropoietin, and other autoimmune phenomenon

Other Causes of Underproduction Anemias

- Marrow replacement (tumors, granulomatous disease; so-called myelophthisic anemias), renal failure, endocrine disorders, liver failure

Polycythemia

Polycythemia denotes an abnormally high red cell count, usually with a corresponding increase in the hemoglobin level. It may be relative when there is hemoconcentration due to decreased plasma volume, or absolute when there is an increase in the total red cell mass. *Relative polycythemia* results from dehydration, such as occurs with deprivation of water, prolonged vomiting or diarrhea, or excessive use of diuretics. It is also associated with an obscure condition of unknown etiology called stress polycythemia, or Gaisböck syndrome. Affected individuals are usually hypertensive, obese, and anxious ("stressed"). *Absolute polycythemia* is *primary* when it results from an intrinsic abnormality of hematopoietic precursors and *secondary* when the red cell progenitors are responding to increased levels of erythropoietin. A pathophysiologic classification of polycythemia divided along these lines is given in Table 14-8.

The most common cause of primary polycythemia is *polycythemia vera*, a myeloproliferative disorder associated with mutations that lead to erythropoietin-independent growth of red cell progenitors (Chapter 13). Much less commonly, primary polycythemia results from familial mutations in the erythropoietin receptor that induce erythropoietin-independent receptor activation. One such individual won Olympic gold medals in cross-country skiing, having benefited from this natural form of blood doping! Secondary polycythemia may be caused by compensatory or pathologic increases in erythropoietin secretion. Causes of the latter include erythropoietin-secreting tumors and rare, but illustrative, inherited defects that lead to the stabilization of HIF-1α, a hypoxia-induced factor that stimulates the transcription of the erythropoietin gene.

Bleeding Disorders: Hemorrhagic Diatheses

Excessive bleeding can result from (1) increased fragility of vessels, (2) platelet deficiency or dysfunction, and (3) derangement of coagulation, alone or in combination. Before discussing specific bleeding disorders, it is helpful to review the common laboratory tests used in the evaluation of a bleeding diathesis. The normal hemostatic response involves the blood vessel wall, the platelets, and the clotting cascade (Chapter 4). Tests used to evaluate different aspects of hemostasis are the following:

- *Prothrombin time (PT).* This test assesses the extrinsic and common coagulation pathways. The clotting of plasma after addition of an exogenous source of tissue thromboplastin (e.g., brain extract) and Ca^{2+} ions is measured in seconds. A prolonged PT can result from deficiency or dysfunction of factor V, factor VII, factor X, prothrombin, or fibrinogen.
- *Partial thromboplastin time (PTT).* This test assesses the intrinsic and common clotting pathways. The clotting of plasma after addition of kaolin, cephalin, and Ca^{2+} ions is measured in seconds. Kaolin activates the contact-dependent factor XII, and cephalin substitutes for platelet phospholipids. Prolongation of the PTT can be due to deficiency or dysfunction of factors V, VIII, IX, X, XI, or XII, prothrombin, or fibrinogen, or to interfering antibodies to phospholipid (Chapter 4).
- *Platelet counts.* These are obtained on anticoagulated blood using an electronic particle counter. The reference range is 150×10^3 to 300×10^3 platelets/μL. Abnormal platelet counts are best confirmed by inspection of a peripheral blood smear, in that clumping of platelets can cause spurious "thrombocytopenia" during automated counting, and high counts may be indicative of a myeloproliferative disorder, such as essential thrombocythemia (Chapter 13).
- *Tests of platelet function.* At present, no single test provides an adequate assessment of the complex functions of platelets. Specialized tests that can be useful in particular clinical settings include tests of platelet aggregation, which measure the ability of platelets to aggregate in response to agonists like thrombin; and quantitative and qualitative tests of von Willebrand factor, which plays an important role in platelet adhesion to the extracellular matrix (Chapter 4). An older test, the bleeding time, has some value but is time-consuming and difficult to standardize and is therefore performed infrequently. Newer instrument-based assays that provide quantitative measures of platelet function show promise but remain imperfect at predicting bleeding risk, presumably because of difficulties in simulating in vivo clotting in the laboratory.

More specialized tests are available to measure the levels of specific clotting factors, fibrinogen, fibrin split products, and the presence of circulating anticoagulants.

Table 14-8 Pathophysiologic Classification of Polycythemia

Relative
Reduced plasma volume (hemoconcentration)
Absolute
Primary (Low Erythropoietin)
Polycythemia vera
Inherited erythropoietin receptor mutations (rare)
Secondary (High Erythropoietin)
Compensatory
Lung disease
High-altitude living
Cyanotic heart disease
Paraneoplastic
Erythropoietin-secreting tumors (e.g., renal cell carcinoma, hepatocellular carcinoma, cerebellar hemangioblastoma)
Hemoglobin mutants with high O_2 affinity
Inherited defects that stabilize HIF-1α
Chuvash polycythemia (homozygous *VHL* mutations)
Prolyl hydroxylase mutations

HIF-1α, Hypoxia-induced factor 1α.

Bleeding Disorders Caused by Vessel Wall Abnormalities

Disorders within this category are relatively common, but do not usually cause serious bleeding problems. Most often, they present with small hemorrhages (petechiae and purpura) in the skin or mucous membranes, particularly the gingivae. On occasion, however, more significant hemorrhages occur into joints, muscles, and subperiosteal

locations, or take the form of menorrhagia, nosebleeds, gastrointestinal bleeding, or hematuria. The platelet count and tests of coagulation (PT, PTT) are usually normal, pointing by exclusion to the underlying problem.

The varied clinical conditions in which abnormalities in the vessel wall cause bleeding include the following:

- *Infections* often induce petechial and purpuric hemorrhages, particularly meningococcemia, other forms of septicemia, infective endocarditis, and several of the rickettsioses. The involved mechanisms include microbial damage to the microvasculature (vasculitis) and disseminated intravascular coagulation. Failure to recognize meningococcemia as a cause of petechiae and purpura can be catastrophic for the patient.
- *Drug reactions* sometimes induce cutaneous petechiae and purpura without causing thrombocytopenia. In many instances the vascular injury is mediated by the deposition of drug-induced immune complexes in vessel walls, which leads to hypersensitivity (*leukocytoclastic*) vasculitis (Chapter 11).
- *Scurvy* and the *Ehlers-Danlos syndrome* are associated with microvascular bleeding that results from collagen defects that weaken vessel walls. The same mechanism may account for the spontaneous purpura that are commonly seen in older adults and the skin hemorrhages that are seen with *Cushing syndrome,* in which the protein-wasting effects of excessive corticosteroid production cause loss of perivascular supporting tissue.
- *Henoch-Schönlein purpura* is a systemic immune disorder of unknown cause that is characterized by a purpuric rash, colicky abdominal pain, polyarthralgia, and acute glomerulonephritis (Chapter 20). All these changes result from the deposition of circulating immune complexes within vessels throughout the body and within the glomerular mesangial regions.
- *Hereditary hemorrhagic telangiectasia* (also known as *Weber-Osler-Rendu syndrome*) is an autosomal dominant disorder that can be caused by mutations in at least five different genes, most of which modulate TGF-β signaling. It is characterized by dilated, tortuous blood vessels with thin walls that bleed readily. Bleeding can occur anywhere, but it is most common under the mucous membranes of the nose (epistaxis), tongue, mouth, and eyes, and throughout the gastrointestinal tract.
- *Perivascular amyloidosis* can weaken blood vessel walls and cause bleeding. This complication is most common with amyloid light-chain (AL) amyloidosis (Chapter 6) and often manifests as mucocutaneous petechiae.

Among these conditions, serious bleeding is most often associated with hereditary hemorrhagic telangiectasia. The bleeding in each is nonspecific, and the diagnosis of these entities is based on the recognition of other more specific associated findings.

Bleeding Related to Reduced Platelet Number: Thrombocytopenia

Reduction in platelet number (*thrombocytopenia*) constitutes an important cause of generalized bleeding. A count less than 100,000 platelets/μL is generally considered to constitute thrombocytopenia. Platelet counts in the range of 20,000 to 50,000 platelets/μL can aggravate posttraumatic bleeding, while platelet counts less than 20,000 platelets/μL may be associated with spontaneous (nontraumatic) bleeding. Bleeding resulting from thrombocytopenia is associated with a normal PT and PTT.

Table 14-9 Causes of Thrombocytopenia

Decreased Production of Platelets
Selective impairment of platelet production
Drug-induced: alcohol, thiazides, cytotoxic drugs
Infections: measles, human immunodeficiency virus (HIV)
Nutritional deficiencies
B_{12}, folate deficiency (megaloblastic leukemia)
Bone marrow failure
Aplastic anemia (see Table 14-7)
Bone marrow replacement
Leukemia, disseminated cancer, granulomatous disease
Ineffective hematopoiesis
Myelodysplastic syndromes (Chapter 13)
Decreased Platelet Survival
Immunologic destruction
Primary autoimmune
Chromic immune thrombocytopenic purpura
Acute immune thrombocytopenic purpura
Secondary autoimmune
Systemic lupus erythematosus, B-cell lymphoid neoplasms
Alloimmune: posttransfusion and neonatal
Drug-associated: quinidine, heparin, sulfa compounds
Infections: HIV, infectious mononucleosis (transient, mild), dengue fever
Nonimmunologic destruction
Disseminated intravascular coagulation
Thrombotic microangiopathies
Giant hemangiomas
Sequestration
Hypersplenism
Dilution
Transfusions

Platelets are critical for hemostasis, in that they form temporary plugs that stop bleeding and promote key reactions in the coagulation cascade (Chapter 4). Spontaneous bleeding associated with thrombocytopenia most often involves small vessels. Common sites for such hemorrhages are the skin and the mucous membranes of the gastrointestinal and genitourinary tracts. Most feared, however, is *intracranial bleeding*, which is a threat to any patient with a markedly depressed platelet count.

The causes of thrombocytopenia fall into four major categories (Table 14-9).

- *Decreased platelet production.* This can result from conditions that depress marrow output generally (such as aplastic anemia and leukemia) or affect megakaryocytes somewhat selectively. Examples of the latter include certain drugs and alcohol, which may suppress platelet production through uncertain mechanisms when taken in large amounts; HIV, which may infect megakaryocytes and inhibit platelet production; and myelodysplastic syndromes (Chapter 13), which may occasionally present with isolated thrombocytopenia.

- *Decreased platelet survival.* This important mechanism of thrombocytopenia can have an immunological or nonimmunologic basis. In *immune thrombocytopenia*, destruction is caused by the deposition of antibodies or immune complexes on platelets. Antibodies to platelets can recognize self-antigens (autoantibodies) or non-self antigens (alloantibodies). Autoimmune thrombocytopenia is discussed in the following section. *Alloantibodies* can arise when platelets are transfused or cross the placenta from the fetus into the pregnant mother. In the latter case, IgG antibodies made in the mother can cause clinically significant thrombocytopenia in the fetus. This is reminiscent of hemolytic disease of the newborn, in which red cells are the target (Chapter 10). The most important nonimmunologic causes are *disseminated intravascular coagulation* and the *thrombotic microangiopathies*, in which unbridled, often systemic, platelet activation reduces platelet life span. Nonimmunologic destruction of platelets may also be caused by *mechanical injury*, such as in individuals with prosthetic heart valves.
- *Sequestration.* The spleen normally sequesters 30% to 35% of the body's platelets, but this can rise to 80% to 90% when the spleen is enlarged, producing moderate degrees of thrombocytopenia.
- *Dilution.* Massive transfusions can produce a dilutional thrombocytopenia. With prolonged blood storage the number of viable platelets decreases; thus, plasma volume and red cell mass are reconstituted by transfusion, but the number of circulating platelets is relatively reduced.

Chronic Immune Thrombocytopenic Purpura (ITP)

Chronic ITP is caused by autoantibody mediated destruction of platelets. It can occur in the setting of a variety of predisposing conditions and exposures (secondary) or in the absence of any known risk factors (primary or idiopathic). The contexts in which chronic ITP occurs secondarily are numerous and include individuals with systemic lupus erythematosus (Chapter 6), HIV infection, and B-cell neoplasms such as chronic lymphocytic leukemia (Chapter 13). The diagnosis of primary chronic ITP is made only after secondary causes are excluded.

Pathogenesis. The autoantibodies, most often directed against platelet membrane glycoproteins IIb-IIIa or Ib-IX, can be demonstrated in the plasma and bound to the platelet surface in about 80% of patients. In the overwhelming majority of cases, the antiplatelet antibodies are of the IgG class.

As in autoimmune hemolytic anemias, antiplatelet antibodies act as opsonins that are recognized by IgG Fc receptors expressed on phagocytes (Chapter 6), leading to increased platelet destruction. The thrombocytopenia is usually markedly improved by splenectomy, indicating that the spleen is the major site of removal of opsonized platelets. The splenic red pulp is also rich in plasma cells, and part of the benefit of splenectomy (a frequent treatment for chronic ITP) may stem from the removal of a source of autoantibodies. In some instances the autoantibodies may also bind to and damage megakaryocytes, leading to decreases in platelet production that further exacerbate the thrombocytopenia.

MORPHOLOGY

The principal changes of thrombocytopenic purpura are found in the spleen, bone marrow, and blood, but they are not specific. Secondary changes related to the bleeding diathesis may be found in any tissue or structure in the body.

The spleen is of normal size. Typically, there is congestion of the sinusoids and enlargement of the splenic follicles, often associated with prominent reactive germinal centers. In many instances scattered megakaryocytes are found within the sinuses, possibly representing a mild form of extramedullary hematopoiesis driven by elevated levels of thrombopoietin. **The marrow reveals a modestly increased number of megakaryocytes**. Some are apparently immature, with large, nonlobulated, single nuclei. These findings are not specific but merely reflect accelerated thrombopoiesis, being found in most forms of thrombocytopenia resulting from increased platelet destruction. The importance of bone marrow examination is to rule out thrombocytopenias resulting from bone marrow failure or other primary bone marrow disorders. The secondary changes relate to the hemorrhages that are dispersed throughout the body. The **peripheral blood often reveals abnormally large platelets** (megathrombocytes), which are a sign of accelerated thrombopoiesis.

Clinical Features

Chronic ITP occurs most commonly in adult women younger than 40 years of age. The female-to-male ratio is 3:1. It is often insidious in onset and is characterized by bleeding into the skin and mucosal surfaces. Cutaneous bleeding is seen in the form of pinpoint hemorrhages (*petechiae*), which are especially prominent in the dependent areas where the capillary pressure is higher. Petechiae can become confluent, giving rise to *ecchymoses.* Often there is a history of easy bruising, nosebleeds, bleeding from the gums, and hemorrhages into soft tissues from relatively minor trauma. The disease may manifest first with melena, hematuria, or excessive menstrual flow. Subarachnoid hemorrhage and intracerebral hemorrhage are serious and sometimes fatal complications, but fortunately they are rare in treated patients. Splenomegaly and lymphadenopathy are uncommon in primary disease, and their presence should lead one to consider other diagnoses, such as ITP secondary to a B-cell neoplasm.

The clinical signs and symptoms are not specific but rather reflective of the thrombocytopenia. The findings of a low platelet count, normal or increased megakaryocytes in the bone marrow, and large platelets in the peripheral blood are taken as presumptive evidence of accelerated platelet destruction. The PT and PTT are normal. Tests for platelet autoantibodies are not widely available. Therefore, the diagnosis is one of exclusion and can be made only after other causes of thrombocytopenia (such as those listed in Table 14-9) have been ruled out.

Almost all patients respond to glucocorticoids (which inhibit phagocyte function), but many eventually relapse. Those with moderately severe thrombocytopenia (platelet counts > 30,000/mL) can be followed carefully, and some of these individuals may have spontaneous remissions over a period of a year or more. In individuals with severe thrombocytopenia, splenectomy normalizes the platelet

count in about two thirds of patients, but with the attendant increased risk of bacterial sepsis. Immunomodulatory agents such as intravenous immunoglobulin or anti-CD20 antibody (rituximab) are often effective in patients who relapse after splenectomy or for whom splenectomy is contraindicated. Peptides that mimic the effects of thrombopoietin (so-called *TPO-mimetics*) are also effective in stimulating platelet production and improving platelet counts.

Acute Immune Thrombocytopenic Purpura

Like chronic ITP, this condition is caused by autoantibodies to platelets, but its clinical features and course are distinct. Acute ITP is mainly a disease of childhood occurring with equal frequency in both sexes. Symptoms appear abruptly, often 1 to 2 weeks after a self-limited viral illness, which appears to trigger the development of autoantibodies through uncertain mechanisms. Unlike chronic ITP, acute ITP is self-limited, usually resolving spontaneously within 6 months. Glucocorticoids are given only if the thrombocytopenia is severe. In about 20% of children, usually those without a viral prodrome, thrombocytopenia persists; these less fortunate children have a childhood form of chronic ITP that follows a course similar to the adult disease.

Drug-Induced Thrombocytopenia

Drugs can induce thrombocytopenia through direct effects on platelets and secondary to immunologically mediated platelet destruction. The drugs most commonly implicated are quinine, quinidine, and vancomycin, all of which bind platelet glycoproteins and in one way or another create antigenic determinants that are recognized by antibodies. Much more rarely, drugs induce true autoantibodies through unknown mechanisms. Thrombocytopenia, which may be severe, is also a common consequence of platelet inhibitory drugs that bind glycoprotein IIb/IIIa; it is hypothesized that these drugs induce conformational changes in glycoprotein IIb/IIIa and create an immunogenic epitope.

Heparin-induced thrombocytopenia (HIT) has a distinctive pathogenesis and is of particular importance because of its potential for severe clinical consequences. Thrombocytopenia occurs in about 5% of persons receiving heparin and is of two types:

- Type I thrombocytopenia occurs rapidly after the onset of therapy and is of little clinical importance, sometimes resolving despite the continuation of therapy. It most likely results from a direct platelet-aggregating effect of heparin.
- Type II thrombocytopenia is less common but of much greater clinical significance. It occurs 5 to 14 days after therapy begins (or sooner if the person has been sensitized to heparin) and, paradoxically, often leads to life-threatening venous and arterial thrombosis. This severe form of HIT is caused by antibodies that recognize complexes of heparin and platelet factor 4, which is a normal component of platelet granules. Binding of antibody to these complexes activates platelets and promotes thrombosis, even in the setting of thrombocytopenia. Unless therapy is immediately discontinued and an alternative nonheparin anticoagulant instituted, clots within large arteries may lead to vascular insufficiency and limb loss, and emboli from deep venous thrombosis can cause fatal pulmonary thromboembolism. The risk of severe HIT is lowered, but not completely eliminated, by the use of low-molecular-weight heparin preparations. Unfortunately, once severe HIT develops even low-molecular-weight heparins exacerbate the thrombotic tendency and must be avoided.

HIV-Associated Thrombocytopenia

Thrombocytopenia is one of the most common hematologic manifestations of HIV infection. Both impaired platelet production and increased destruction contribute. CD4 and CXCR4, the receptor and coreceptor, respectively, for HIV, are found on megakaryocytes, allowing these cells to be infected. HIV-infected megakaryocytes are prone to apoptosis and their ability to produce platelets is impaired. HIV infection also causes B-cell hyperplasia and dysregulation, which predisposes to the development of autoantibodies. In some instances the antibodies are directed against platelet membrane glycoprotein IIb-III complexes. As in other immune cytopenias, the autoantibodies opsonize platelets, promoting their destruction by mononuclear phagocytes in the spleen and elsewhere. The deposition of immune complexes on platelets may also contribute to the accelerated loss of platelets in some patients who are HIV infected.

Thrombotic Microangiopathies: Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic-Uremic Syndrome (HUS)

The term *thrombotic microangiopathy* encompasses a spectrum of clinical syndromes that includes TTP and HUS. They are caused by insults that lead to excessive activation of platelets, which deposit as thrombi in small blood vessels.

According to its original description, TTP was defined as the pentad of fever, thrombocytopenia, microangiopathic hemolytic anemia, transient neurologic deficits, and renal failure. HUS is also associated with microangiopathic hemolytic anemia and thrombocytopenia but is distinguished by the absence of neurologic symptoms, the prominence of acute renal failure, and its frequent occurrence in children. With time, experience, and increased mechanistic insight, however, these distinctions have blurred. Many adult patients with "TTP" lack one or more of the five criteria, and some patients with "HUS" have fever and neurologic dysfunction.

In both conditions, intravascular thrombi cause a *microangiopathic hemolytic anemia* and widespread *organ dysfunction*, and the attendant consumption of platelets leads to thrombocytopenia. It is believed that the varied clinical manifestations of TTP and HUS are related to differing proclivities for thrombus formation in tissues. While disseminated intravascular coagulation (discussed later) and thrombotic microangiopathies share features such as microvascular occlusion and microangiopathic hemolytic anemia, they are pathogenically distinct. In TTP and HUS (unlike in disseminated intravascular coagulation), activation of the coagulation cascade is not of primary importance, and hence laboratory tests of coagulation, such as the PT and PTT, are usually normal.

Table 14-10 Thrombotic Microangiopathies: Causes and Associations

Thrombotic Thrombocytopenic Purpura
Deficiency of ADAMTS13
Inherited Acquired (autoantibodies)
Hemolytic Uremic Syndrome
Typical: *Escherichia coli* strain 0157:H7 infection
Endothelial damage by Shiga-like toxin
Atypical: alternative complement pathway inhibitor deficiencies
(complement factor H, membrane cofactor protein (CD46), or factor I) Inherited Acquired (autoantibodies)
Miscellaneous associations
Drugs (cyclosporine, chemotherapeutic agents) Radiation, bone marrow transplantation Other infections (HIV, pneumococcal sepsis) Conditions associated with autoimmunity (systemic lupus erythematosus, HIV infection, lymphoid neoplasms)

HIV, Human immunodeficiency virus.

Although certain features of the various thrombotic microangiopathies overlap, the triggers for the pathogenic platelet activation are distinctive and provide a more satisfying and clinically relevant way of thinking about these disorders; these are summarized in Table 14-10. **TTP is usually associated with a deficiency in a plasma enzyme called *ADAMTS13***, also designated "vWF metalloprotease." ADAMTS13 normally degrades very high-molecular-weight multimers of von Willebrand factor (vWF). In its absence, these multimers accumulate in plasma and tend to promote platelet activation and aggregation. Superimposition of endothelial cell injury (caused by some other condition) may further promote the formation of platelet microaggregates, thus initiating or exacerbating clinically evident TTP.

The deficiency of ADAMTS13 can be inherited or acquired. In the acquired form, an autoantibody that inhibits the metalloprotease activity of ADAMTS13 is present. Less commonly, patients inherit an inactivating mutation in *ADAMTS13*. In those with hereditary ADAMTS13 deficiency, the onset is often delayed until adolescence and the symptoms are episodic. Thus, factors other than ADAMTS13 (e.g., some superimposed vascular injury or prothrombotic state) must be involved in triggering full-blown TTP.

TTP is an important diagnosis to consider in any patient presenting with thrombocytopenia and microangiopathic hemolytic anemia, because delays in diagnosis can be fatal. With plasma exchange, which removes autoantibodies and provides functional ADAMTS13, TTP (which once was uniformly fatal) can be treated successfully in more than 80% of patients.

In contrast, HUS is associated with normal levels of ADAMTS13 and is initiated by several other distinct defects. "Typical" HUS is strongly associated with infectious gastroenteritis caused by *Escherichia coli* strain O157:H7, which elaborates a Shiga-like toxin. This toxin is absorbed from the inflamed gastrointestinal mucosa into the circulation, where it alters endothelial cell function in some manner that results in platelet activation and aggregation. Children and older adults are at highest risk. Those affected present with bloody diarrhea, and a few days later HUS makes its appearance. With appropriate supportive care complete recovery is possible, but irreversible renal damage and death can occur in more severe cases.

"Atypical" HUS is often associated with defects in complement factor H, membrane cofactor protein (CD46), or factor I, three proteins that normally act to prevent excessive activation of the alternative complement pathway. Deficiencies of these proteins can be caused by inherited defects or acquired inhibitory autoantibodies and are associated with a remitting, relapsing course. Unlike TTP, the basis for the platelet activation in typical and atypical HUS is unclear. Therapeutic antibodies that inhibit the activation of the complement factor C5 are effective in preventing thrombosis in patients with inherited deficiencies of complement regulatory proteins, proving that excessive complement activation underlies the pathogenesis of this form of HUS. Similarly, immunosuppression can be beneficial to patients with inhibitory antibodies against complement regulatory factors. Typical HUS is treated supportively. Patients who survive the acute insult usually recover, but some have permanent renal damage and eventually require dialysis or renal transplantation. The impact of HUS and TTP on the kidneys is discussed further in Chapter 20.

Thrombotic microangiopathies resembling HUS can also be seen following exposures to other agents that damage endothelial cells (e.g., certain drugs and radiation therapy). The prognosis in these settings is guarded, because the HUS is often complicated by chronic, life-threatening conditions.

Bleeding Disorders Related to Defective Platelet Functions

Qualitative defects of platelet function can be inherited or acquired. Several inherited disorders characterized by abnormal platelet function and normal platelet count have been described. A brief discussion of these rare diseases is warranted because they provide excellent models for investigating the molecular mechanisms of platelet function.

Inherited disorders of platelet function can be classified into three pathogenically distinct groups: (1) defects of adhesion, (2) defects of aggregation, and (3) disorders of platelet secretion (release reaction).

- *Bernard-Soulier syndrome* illustrates the consequences of defective adhesion of platelets to subendothelial matrix. Bernard-Soulier syndrome is caused by an inherited deficiency of the platelet membrane glycoprotein complex Ib-IX. This glycoprotein is a receptor for vWF and is essential for normal platelet adhesion to the subendothelial extracellular matrix (Chapter 4). Affected patients have a variable, often severe, bleeding tendency.
- Bleeding due to *defective platelet aggregation* is exemplified by *Glanzmann thrombasthenia,* which is also transmitted as an autosomal recessive trait. Thrombasthenic platelets fail to aggregate in response to adenosine diphosphate (ADP), collagen, epinephrine, or thrombin because of deficiency or dysfunction of glycoprotein IIb-IIIa, an integrin that participates in "bridge formation" between platelets by binding fibrinogen. The associated bleeding tendency is often severe.

- *Disorders of platelet secretion* are characterized by the defective release of certain mediators of platelet activation, such as thromboxanes and granule-bound ADP. The biochemical defects underlying these so-called *storage pool disorders* are varied, complex, and beyond the scope of our discussion.

Among the *acquired defects* of platelet function, two are clinically significant. The first is caused by ingestion of *aspirin and other nonsteroidal anti-inflammatory drugs*. Aspirin is a potent, irreversible inhibitor of the enzyme cyclooxygenase, which is required for the synthesis of thromboxane A_2 and prostaglandins (Chapter 3). These mediators play important roles in platelet aggregation and subsequent release reactions (Chapter 4). The antiplatelet effects of aspirin form the basis for its use in the prophylaxis of coronary thrombosis (Chapter 12). *Uremia* (Chapter 20) is the second condition exemplifying an acquired defect in platelet function. The pathogenesis of platelet dysfunction in uremia is complex and involves defects in adhesion, granule secretion, and aggregation.

Hemorrhagic Diatheses Related to Abnormalities in Clotting Factors

Inherited or acquired deficiencies of virtually every coagulation factor have been reported as causes of bleeding diatheses. Bleeding due to isolated coagulation factor deficiencies most commonly manifests as *large posttraumatic ecchymoses or hematomas,* or *prolonged bleeding* after a laceration or any form of surgical procedure. Unlike bleeding seen with thrombocytopenia, bleeding due to coagulation factor deficiencies often occurs into the gastrointestinal and urinary tracts and into weight-bearing joints (hemarthrosis). Typical stories include the patient who oozes blood for days after a tooth extraction or who develops a hemarthrosis after minor stress on a knee joint.

Hereditary deficiencies typically affect a single clotting factor. The most common and important inherited deficiencies of coagulation factors affect factor VIII (hemophilia A), and factor IX (hemophilia B). Deficiencies of vWF (von Willebrand disease) are also discussed here, as this factor influences both coagulation and platelet function. Rare inherited deficiencies of each of the other coagulation factors have also been described.

Acquired deficiencies usually involve multiple coagulation factors and can be based on decreased protein synthesis or a shortened half-life. Vitamin K deficiency (Chapter 9) results in the impaired synthesis of factors II, VII, IX, X and protein C. Many of these factors are made in the liver and are therefore deficient in severe parenchymal liver disease. Alternatively, in disseminated intravascular coagulation, multiple coagulation factors are consumed and are therefore deficient. Acquired deficiencies of single factors occur, but they are rare. These are usually caused by inhibitory autoantibodies.

The Factor VIII-vWF Complex

The two most common inherited disorders of bleeding, hemophilia A and von Willebrand disease, are caused by qualitative or quantitative defects involving factor VIII and vWF, respectively. Before we discuss these disorders it will be helpful to review the structure and function of these two proteins, which exist together in the plasma as part of a single large complex.

Factor VIII and vWF are encoded by separate genes and are synthesized in different cells. Factor VIII is an essential cofactor of factor IX, which converts factor X to factor Xa (Fig. 14-26; Chapter 4). It is made in several tissues; sinusoidal endothelial cells and Kupffer cells in the liver seem to be major sources. Once factor VIII reaches the

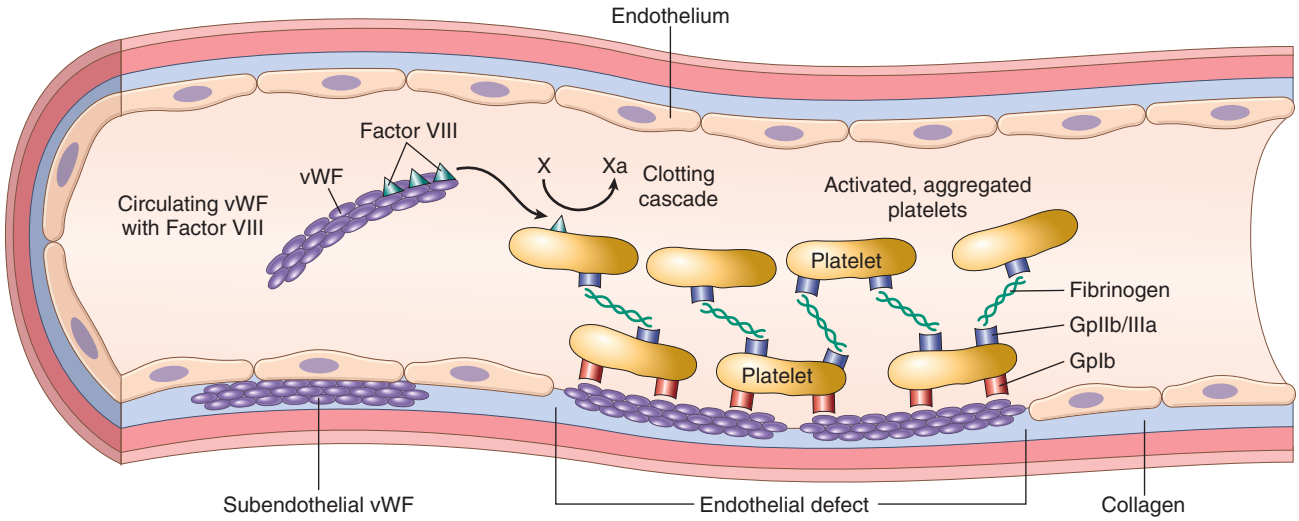

Figure 14-26 Structure and function of factor VIII-von Willebrand factor (vWF) complex. Factor VIII is synthesized in the liver and kidney, and vWF is made in endothelial cells and megakaryocytes. The two associate to form a complex in the circulation. vWF is also present in the subendothelial matrix of normal blood vessels and the α-granules of platelets. Following endothelial injury, exposure of subendothelial vWF causes adhesion of platelets, primarily via the glycoprotein Ib (GpIb) platelet receptor. Circulating vWF and vWF released from the α-granules of activated platelets can bind exposed subendothelial matrix, further contributing to platelet adhesion and activation. Activated platelets form hemostatic aggregates; fibrinogen participates in aggregation through bridging interactions with the glycoprotein IIb/IIIa (GpIIb/IIIa) platelet receptor. Factor VIII takes part in the coagulation cascade as a cofactor in the activation of factor X on the surface of activated platelets.

circulation, it binds to vWF, which is produced by endothelial cells and, to a lesser degree, by megakaryocytes, which are the source of the vWF that is found in platelet α-granules. vWF stabilizes factor VIII, which has a half-life of about 2.4 hours when free and 12 hours when bound to vWF in the circulation.

Circulating vWF exists as multimers containing as many as 100 subunits that can exceed 20×10^6 daltons in molecular mass. In addition to factor VIII, these multimers interact with several other proteins involved in hemostasis, including collagen, heparin, and possibly platelet membrane glycoproteins. The most important function of vWF is to promote the adhesion of platelets to the subendothelial matrix. This occurs through bridging interactions between platelet glycoprotein Ib-IX, vWF, and matrix components such as collagen. Some vWF is secreted from endothelial cells directly into the subendothelial matrix, where it lies ready to promote platelet adhesion if the endothelial lining is disrupted (Fig. 14-26). Endothelial cells and platelets also release vWF into the circulation. Upon vascular injury, this second pool of vWF binds collagen in the subendothelial matrix to further augment platelet adhesion. vWF multimers may also promote platelet aggregation by binding to activated GpIIb/IIIa integrins; this activity may be of particular importance under conditions of high shear stress (such as occurs in small vessels).

Factor VIII and vWF protein levels are measured by immunological techniques. Factor VIII function is measured specifically by performing coagulation assays with mixtures of patient plasma and factor VIII-deficient plasma. vWF function is assessed using the ristocetin agglutination test. This assay is performed by mixing the patient's plasma with formalin-fixed platelets and ristocetin, a small molecule that binds and "activates" vWF. Ristocetin induces multivalent vWF multimers to bind platelet glycoprotein Ib-IX and form interplatelet "bridges." The resulting clumping (agglutination) of platelets is measured in a device called an aggregometer. Thus, the degree to which patient plasma promotes ristocetin-dependent platelet agglutination reflects the vWF activity of the sample.

Von Willebrand Disease

Von Willebrand disease is the most common inherited bleeding disorder of humans, affecting about 1% of adults in the United States. The bleeding tendency is usually mild and often goes unnoticed until some hemostatic stress, such as surgery or a dental procedure, reveals its presence. The most common presenting symptoms are spontaneous bleeding from mucous membranes (e.g., epistaxis), excessive bleeding from wounds, or menorrhagia. It is usually transmitted as an autosomal dominant disorder, but rare autosomal recessive variants also exist.

Von Willebrand disease is clinically and molecularly heterogeneous; several hundred vWF variants have been described, few of which have been formally proven to be disease-causing. Three broad categories of von Willebrand disease are recognized, each with a range of phenotypes:

- **Type 1 and type 3 von Willebrand disease are associated with *quantitative defects* in vWF. Type 1, an autosomal dominant disorder characterized by a mild to moderate vWF deficiency**, accounts for about 70% of all cases. Incomplete penetrance and variable expressivity are commonly observed, but it generally is associated with mild disease. **Type 3 (an autosomal recessive disorder) is associated with very low levels of vWF and correspondingly severe clinical manifestations.** Because a severe deficiency of vWF has a marked effect on the stability of factor VIII, some of the bleeding characteristics resemble those seen in hemophilia. Type 1 disease is associated with a spectrum of mutations, including point substitutions that interfere with maturation of the vWF protein or that result in rapid clearance from the plasma. Type 3 disease is usually caused by deletions or frameshift mutations involving both alleles.
- **Type 2 von Willebrand disease is characterized by qualitative defects in vWF**; there are several subtypes, of which type 2A is the most common. It is inherited as an autosomal dominant disorder. vWF is expressed in normal amounts, but missense mutations are present that lead to defective multimer assembly. Large and intermediate multimers, representing the most active forms of vWF, are missing from plasma. Type 2 von Willebrand disease accounts for 25% of all cases and is associated with mild to moderate bleeding.

Patients with von Willebrand disease have defects in platelet function despite a normal platelet count. The plasma level of active vWF, measured as the ristocetin cofactor activity, is reduced. Because vWF stabilizes factor VIII, a deficiency of vWF gives rise to a secondary decrease in factor VIII levels. This may be reflected by a prolongation of the PTT in von Willebrand disease types 1 and 3. However, except in rare type 3 patients, adverse complications typical of severe factor VIII deficiency, such as bleeding into the joints, are not seen.

Even within families in which a single defective vWF allele is segregating, wide variability in clinical expression is common. This is due in part to modifying genes that influence circulating levels of vWF, which show a wide range in normal populations. Persons with von Willebrand disease facing hemostatic challenges (dental work, surgery) can be treated with desmopressin, which stimulates vWF release, or with infusions of plasma concentrates containing factor VIII and vWF.

Hemophilia A (Factor VIII Deficiency)

Hemophilia A, the most common hereditary disease associated with life-threatening bleeding, is caused by mutations in factor VIII, an essential cofactor for factor IX in the coagulation cascade. Hemophilia A is inherited as an X-linked recessive trait and thus affects mainly males and homozygous females. Rarely, excessive bleeding occurs in heterozygous females, presumably as a result of inactivation of the X chromosome bearing the normal factor VIII allele by chance in most cells (unfavorable lyonization). About 30% of patients have no family history; their disease is caused by new mutations.

Hemophilia A exhibits a wide range of clinical severity that correlates well with the level of factor VIII activity. Those with less than 1% of normal levels have severe disease; those with 2% to 5% of normal levels have moderately severe disease; and those with 6% to 50% of normal levels have mild disease. The varying degrees of factor VIII deficiency are largely explained by heterogeneity in the causative mutations. As with β-thalassemia, the genetic lesions include deletions, nonsense mutations that create stop codons, and mutations that cause errors in mRNA

splicing. The most severe deficiencies result from an inversion involving the X chromosome that completely abolishes the synthesis of factor VIII. Less commonly, severe hemophilia A is associated with point mutations in factor VIII that impair the function of the protein. In such cases factor VIII protein levels may be normal by immunoassay. Mutations permitting some active factor VIII to be synthesized are associated with mild to moderate disease. The disease in such patients may be modified by other genetic factors that influence factor VIII expression levels, which vary widely in normal individuals.

In all symptomatic cases there is a tendency toward easy bruising and massive hemorrhage after trauma or operative procedures. In addition, "spontaneous" hemorrhages frequently occur in regions of the body that are susceptible to trauma, particularly the joints, where they are known as *hemarthroses.* Recurrent bleeding into the joints leads to progressive deformities that can be crippling. Petechiae are characteristically absent.

Patients with hemophilia A have a prolonged PTT and a normal PT, results that point to an abnormality of the intrinsic coagulation pathway. Factor VIII-specific assays are required for diagnosis. As explained in Chapter 4, the bleeding diathesis reflects the pre-eminent role of the factor VIIIa/factor IXa complex in activation of factor X in vivo. The precise explanation for the tendency of hemophiliacs to bleed at particular sites (joints, muscles, and the central nervous system) remains uncertain.

Hemophilia A is treated with infusions of recombinant factor VIII. About 15% of patients with severe hemophilia A develop antibodies that bind and inhibit factor VIII, probably because the protein is perceived as foreign, having never been "seen" by the immune system. These antibody inhibitors can be a very difficult therapeutic challenge. Before the development of recombinant factor VIII therapy, thousands of hemophiliacs received plasma-derived factor VIII concentrates containing HIV, and many developed AIDS (Chapter 6). The risk of HIV transmission has been eliminated but tragically too late for an entire generation of hemophiliacs. Efforts to develop somatic gene therapy for hemophilia are ongoing.

Hemophilia B (Christmas Disease, Factor IX Deficiency)

Severe factor IX deficiency produces a disorder clinically indistinguishable from factor VIII deficiency (hemophilia A). This should not be surprising, given that factors VIII and IX function together to activate factor X. A wide spectrum of mutations involving the gene that encodes factor IX is found in hemophilia B. Like hemophilia A, it is inherited as an X-linked recessive trait and shows variable clinical severity. In about 15% of these patients, factor IX protein is present but is nonfunctional. As with hemophilia A, the PTT is prolonged and the PT is normal. Diagnosis of Christmas disease (named after the first patient identified with this condition, and not the holiday) is possible only by assay of the factor levels. The disease is treated with infusions of recombinant factor IX.

Disseminated Intravascular Coagulation (DIC)

DIC is an acute, subacute, or chronic thrombohemorrhagic disorder characterized by the excessive activation of coagulation and the formation of thrombi in the microvasculature of the body. It occurs as a secondary complication of many different disorders. Sometimes the coagulopathy is localized to a specific organ or tissue. As a consequence of the thrombotic diathesis there is consumption of platelets, fibrin, and coagulation factors and, secondarily, activation of fibrinolysis. DIC can present with signs and symptoms relating to the tissue hypoxia and infarction caused by the myriad microthrombi; with hemorrhage caused by the depletion of factors required for hemostasis and the activation of fibrinolytic mechanisms; or both.

Etiology and Pathogenesis. At the outset, it must be emphasized that DIC is not a primary disease. It is a coagulopathy that occurs in the course of a variety of clinical conditions. In discussing the general mechanisms underlying DIC, it is useful to briefly review the normal process of blood coagulation and clot removal (Chapter 4).

Clotting in vivo is thought to be initiated by exposure of tissue factor, which combines with factor VII to activate both factor X directly and to activate factor IX. Activation of factor X leads to the generation of *thrombin*, the central player in clotting. At sites where the endothelium is disrupted, thrombin converts fibrinogen to fibrin, feeds back to activate factors IX, VIII, and V, stimulates fibrin cross-linking, inhibits fibrinolysis, and activates platelets, all of which augment the formation of a stable clot. To prevent runaway clotting, this process must be sharply limited to the site of tissue injury. Remarkably, as thrombin is swept away in the bloodstream and encounters uninjured vessels, it is converted to an anticoagulant through binding to *thrombomodulin*, a protein found on the surface of endothelial cells. The thrombin-thrombomodulin complex activates protein C, which is an important inhibitor of factor V and factor VIII. Other activated coagulation factors are removed from the circulation by the liver, and as you will recall, the blood also contains several potent fibrinolytic factors, such as plasmin. These and additional checks and balances normally ensure that just enough clotting occurs at the right place and time.

From this brief review it should be clear that DIC could result from pathologic activation of coagulation or the impairment of clot-inhibiting mechanisms. Because the latter rarely constitute primary mechanisms of DIC, we will focus on the abnormal initiation of clotting.

Two major mechanisms trigger DIC: (1) release of tissue factor or other, poorly characterized procoaagulants, into the circulation, and (2) widespread injury to the endothelial cells. Procoagulants such as tissue factor can be derived from a variety of sources, such as the placenta in obstetric complications or tissues injured by trauma or burns. Mucus released from certain adenocarcinomas may also act as procoagulants by directly activate factor X.

Endothelial injury can initiate DIC in several ways. Injuries that cause endothelial cell necrosis expose the subendothelial matrix, leading to the activation of platelets and the coagulation pathway. However, even subtle endothelial injuries can unleash procoagulant activity. One mediator of endothelial injury is TNF, which is implicated in DIC occurring with sepsis. TNF induces endothelial cells to express tissue factor on their cell surfaces and to decrease the expression of thrombomodulin, shifting the checks and balances that govern hemostasis towards coagulation. In addition, TNF up-regulates the expression of adhesion

molecules on endothelial cells, thereby promoting the adhesion of leukocytes, which can damage endothelial cells by releasing reactive oxygen species and preformed proteases. Widespread endothelial injury may also be produced by deposition of antigen-antibody complexes (e.g., systemic lupus erythematosus), temperature extremes (e.g., heat stroke, burns), or microorganisms (e.g., meningococci, rickettsiae). Even subtle endothelial injury can unleash procoagulant activity by enhancing membrane expression of tissue factor.

DIC is most likely to be associated with obstetric complications, malignant neoplasms, sepsis, and major trauma. The triggers in these conditions are often multiple and interrelated. For example, in bacterial infections *endotoxins* can inhibit the endothelial expression of thrombomodulin directly or indirectly by stimulating immune cells to make TNF, and can also activate factor XII. *Antigen-antibody complexes* formed in response to the infection can activate the classical complement pathway, giving rise to complement fragments that secondarily activate both platelets and granulocytes. In *massive trauma, extensive surgery,* and *severe burns,* the major trigger is the release of procoagulants such as tissue factor. In *obstetric conditions*, procoagulants derived from the placenta, dead retained fetus, or amniotic fluid may enter the circulation. *Hypoxia, acidosis, and shock,* which often coexist in very ill patients, can also cause widespread endothelial injury, and supervening infections can complicate the problems further. *Among cancers, acute promyelocytic leukemia and adenocarcinomas* of the lung, pancreas, colon, and stomach are most frequently associated with DIC.

The possible consequences of DIC are twofold (Fig. 14-27).

- *Widespread deposition of fibrin* within the microcirculation. This leads to *ischemia* of the more severely affected or more vulnerable organs and a *microangiopathic hemolytic anemia*, which results from the fragmentation of red cells as they squeeze through the narrowed microvasculature.
- Consumption of platelets and clotting factors and the activation of plasminogen, leading to a *hemorrhagic diathesis*. Plasmin not only cleaves fibrin, but it also digests factors V and VIII, thereby reducing their concentration further. In addition, fibrin degradation products resulting from fibrinolysis inhibit platelet aggregation, fibrin polymerization, and thrombin.

MORPHOLOGY

Thrombi are most often found in the brain, heart, lungs, kidneys, adrenals, spleen, and liver, in decreasing order of frequency, but any tissue can be affected. Affected kidneys may have small thrombi in the glomeruli that evoke only reactive swelling of endothelial cells or, in severe cases, microinfarcts or even **bilateral renal cortical necrosis**. Numerous fibrin thrombi may be found in alveolar capillaries, sometimes associated with pulmonary edema and fibrin exudation, creating "hyaline membranes" reminiscent of acute respiratory distress syndrome (Chapter 15). In the central nervous system, fibrin thrombi can cause microinfarcts, occasionally complicated by simultaneous hemorrhage, which can sometimes lead to variable neurologic signs and symptoms. The manifestations in the endocrine glands are of considerable interest. In meningococcemia, fibrin thrombi within the microcirculation of the adrenal cortex are the probable basis for the massive adrenal hemorrhages seen in **Waterhouse-Friderichsen syndrome** (Chapter 24). An unusual form of DIC occurs in association with giant hemangiomas (**Kasabach-Merritt syndrome**), in which thrombi form within the neoplasm because of stasis and recurrent trauma to fragile blood vessels.

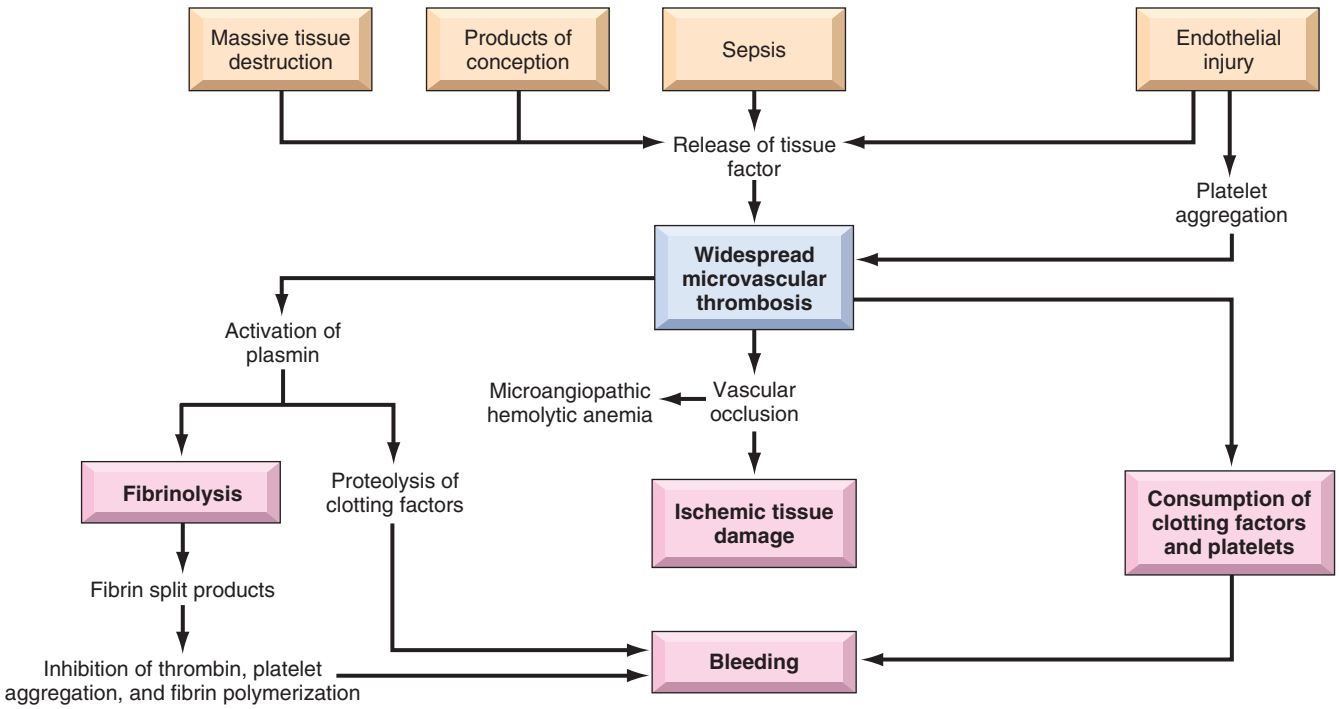

Figure 14-27 Pathophysiology of disseminated intravascular coagulation.

Clinical Features. The onset can be fulminant, as in endotoxic shock or amniotic fluid embolism, or insidious and chronic, as in cases of carcinomatosis or retention of a dead fetus. Overall, about 50% of the affected are obstetric patients having complications of pregnancy. In this setting the disorder tends to be reversible with delivery of the fetus. About 33% of the affected patients have carcinomatosis. The remaining cases are associated with the various entities previously listed.

It is almost impossible to detail all the potential clinical presentations, but a few common patterns are worthy of description. These include *microangiopathic hemolytic anemia*; dyspnea, cyanosis, and respiratory failure; convulsions and coma; oliguria and acute renal failure; and sudden or progressive circulatory failure and shock. In general, acute DIC, associated with obstetric complications or major trauma, for example, is dominated by a bleeding diathesis, whereas chronic DIC, such as occurs in cancer patients, tends to present with thrombotic complications. The diagnosis is based on clinical observation and laboratory studies, including measurement of fibrinogen levels, platelets, the PT and PTT, and fibrin degradation products.

The prognosis is highly variable and largely depends on the underlying disorder. The only definitive treatment is to remove or treat the inciting cause. The management requires meticulous maneuvering between the Scylla of thrombosis and the Charybdis of bleeding diathesis. Administration of anticoagulants or procoagulants has been advocated in specific settings, but not without controversy.

KEY CONCEPTS

Immune Thrombocytopenic Purpura

- Caused by autoantibodies against platelet antigens
- May be triggered by drugs, infections, or lymphomas, or may be idiopathic

Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

- Both manifest with thrombocytopenia, microangiopathic hemolytic anemia, and renal failure; fever and CNS involvement are more typical of TTP.
- *TTP*: Caused by acquired or inherited deficiencies of ADAMTS 13, a plasma metalloprotease that cleaves very-high-molecular-weight multimers of von Willebrand factor (vWF). Deficiency of ADAMTS 13 results in abnormally large vWF multimers that activate platelets.
- *Hemolytic uremic syndrome*: caused by deficiencies of complement regulatory proteins or agents that damage endothelial cells, such as a Shiga-like toxin elaborated by *E. coli* strain O157:H7. The abnormalities initiate platelet activation, platelet aggregation, and microvascular thrombosis.

Von Willebrand Disease

- Autosomal dominant disorder caused by mutations in vWF, a large protein that promotes the adhesion of platelets to subendothelial collagen
- Typically causes a mild to moderate bleeding disorder resembling that associated with thrombocytopenia

Hemophilia

- *Hemophilia A*: X-linked disorder caused by mutations in factor VIII. Affected males typically present with severe bleeding into soft tissues and joints and have a PTT.
- *Hemophilia B*: X-linked disorder caused by mutations in coagulation factor IX. It is clinically identical to hemophilia A.

Disseminated Intravascular Coagulation

- Syndrome in which systemic activation of the coagulation leads to consumption of coagulation factors and platelets
- Can produce bleeding, vascular occlusion and tissue hypoxemia, or both
- Common triggers: sepsis, major trauma, certain cancers, obstetric complications

Complications of Transfusion

Blood products are often rightly called the gift of life, permitting people to survive traumatic injuries and procedures such as hematopoietic stem cell transplantation and complex surgical procedures that would otherwise prove fatal. Over 5 million red cell transfusions are given in US hospitals each year. Thanks to improved screening of donors, blood products (packed red blood cells, platelets, and fresh-frozen plasma) are safer than ever before.

Nevertheless, complications still occur. Most are minor and transient. The most common is referred to as a *febrile nonhemolytic reaction*, which takes the form of fever and chills, sometimes with mild dyspnea, within 6 hours of a transfusion of red cells or platelets. These reactions are thought to be caused by inflammatory mediators derived from donor leukocytes. The frequency of these reactions increases with the storage age of the product and is decreased by measures that limit donor leukocyte contamination. Symptoms respond to antipyretics and are short-lived.

Other transfusion reactions are uncommon or rare, but can have severe and sometimes fatal consequences, and therefore merit discussion.

Allergic Reactions

Severe, potentially fatal allergic reactions may occur when blood products containing certain antigens are given to previously sensitized recipients. These are most likely to occur in patients with IgA deficiency, which has a frequency of 1:300 to 1:500 people. In this instance, the reaction is triggered by IgG antibodies that recognize IgA in the infused blood product. Fortunately, most patients with IgA deficiency do not develop such antibodies, and these severe reactions are rare, occurring in 1 in 20,000 to 1 in 50,000 transfusions. *Urticarial allergic reactions* may be triggered by the presence an allergen in the donated blood product that is recognized by IgE antibodies in the recipient. These are considerably more common, occurring in 1% to 3% of transfusions, but are generally mild. In most instances symptoms respond to antihistamines and do not require discontinuation of the transfusion.

Hemolytic Reactions

***Acute hemolytic reactions* are usually caused by preformed IgM antibodies against donor red cells that fix**

complement. They most commonly stem from an error in patient identification or tube labeling that allows a patient to receive an ABO incompatible unit of blood. Pre-existing high affinity "natural" IgM antibodies, usually against polysaccharide blood group antigens A or B, bind to red cells and rapidly induce complement mediated lysis, intravascular hemolysis, and hemoglobinuria. Fever, shaking chills, and flank pain appear rapidly. The direct Coombs test is typically positive, unless all of the donor red cells have lysed. The signs and symptoms are due to complement activation rather than intravascular hemolysis *per se*, as osmotic lysis of red cells (e.g., by mistakenly infusing red cells and 5% dextrose in water simultaneously) produces hemoglobinuria without any of the other symptoms of a hemolytic reaction. In severe cases the process may rapidly progress to DIC, shock, acute renal failure, and occasionally death.

***Delayed hemolytic reactions* are caused by antibodies that recognize red cell antigens that the recipient was sensitized to previously, for example, through a prior blood transfusion.** These are typically caused by IgG antibodies to foreign protein antigens and are associated with a positive direct Coombs test and laboratory features of hemolysis (e.g., low haptoglobin and elevated LDH). Antibodies to antigens such as Rh, Kell, and Kidd often induce sufficient complement activation to cause severe and potentially fatal reactions identical to those resulting from ABO mismatches. Other antibodies that do not fix complement typically result in red cell opsonization, extravascular hemolysis, and spherocytosis, and are associated with relatively minor signs and symptoms.

Transfusion-Related Acute Lung Injury

TRALI is a severe, frequently fatal complication in which factors in a transfused blood product trigger the activation of neutrophils in the lung microvasculature. The incidence of TRALI is low, probably less than 1 per 10,000 transfusions, but it may occur more frequently in patients with preexisting lung disease. Though its pathogenesis is incompletely understood, current models favor a "two hit" hypothesis. The first is a priming event that leads to increased sequestration and sensitization of neutrophils in the microvasculature of the lung. It is postulated that this event may involve endothelial activation, for example by inflammatory mediators. The primed neutrophils are then activated by a factor present in the transfused blood product, which constitutes the second hit.

A variety of factors have been implicated as "second hits", but the leading candidates are antibodies in the transfused blood product that recognize antigens expressed on neutrophils. By far the most common antibodies associated with TRALI are those that bind major histocompatibility complex (MHC) antigens, particularly MHC class I antigens. These antibodies are often found in multiparous women, who generate such antibodies in response to foreign MHC antigens expressed by the fetus. Rarely, donor antibodies to neutrophil-specific antigens trigger TRALI. Although TRALI has been associated with virtually all plasma-containing blood products, it is more likely to occur following transfusion of products containing high levels of donor antibodies, such as fresh frozen plasma and platelets. The presentation is dramatic, sudden onset respiratory failure, during or soon after a transfusion. Diffuse bilateral pulmonary infiltrates that do not respond to diuretics are seen on chest imaging. Other associated findings include fever, hypotension and hypoxemia. The treatment is largely supportive and the outcome is guarded; mortality is 5% in uncomplicated cases and up to 67% in those who were severely ill. TRALI is important to recognize, because donor products that induce the complication in one patient are much more likely to do so in a second. Indeed, recent measures to exclude multiparous women from plasma donation have resulted in the incidence of TRALI being cut in half.

Infectious Complications

Virtually any infectious agent can be transmitted through blood products, but bacterial and viral infections are most likely to be so. Most *bacterial infections* are caused by skin flora, indicating that the contamination occurred at the time that the product is taken from the donor. Significant bacterial contamination (sufficient to produce symptoms) is much more common in platelet preparations than red cell preparations, due in large part to the fact that platelets (unlike red cells) must be stored at room temperature, conditions that are favorable for bacterial growth. Rates of bacterial infection secondary to platelet transfusion can be as high as 1 in 5000, with infections secondary to red cell transfusions being several orders of magnitude less frequent. Many of the symptoms (fever, chills, hypotension) resemble those of hemolytic and non-hemolytic transfusion reactions, and it may be necessary to start broad-spectrum antibiotics prospectively in symptomatic patients while awaiting laboratory results.

Advances in donor selection, donor screening, and infectious disease testing have dramatically decreased the incidence of viral transmission by blood products. However on rare occasions when the donor is acutely infected but the virus is not yet detectable with current nucleic acid testing technology, there can be transfusion-related transmission of viruses such as HIV, hepatitis C, and hepatitis B. Rates of transmission of HIV, hepatitis C, and hepatitis B are estimated to be 1 in 2 million, 1 in 1 million, and 1 in 500,000, respectively. There also remains a low risk of "exotic" infectious agents such as West Nile virus, trypanosomiasis, and babesiosis.

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